UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/441,443	05/15/95	HOUGHTON	

EXAMINER

HM21/0901

ALISA A HARBIN
CHIRON CORPORATION
INTELLECTUAL PROPERTY - R440
P O BOX 8097
EMERYVILLE CA 94662-8097

ART UNIT	PAPER NUMBER
1643	14

DATE MAILED: 09/01/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/19/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 40-55 is/are pending in the application.
Of the above, claim(s) 49-51 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 40-48 + 52-55 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1643.

2. Claims 40-55 are pending in this application. Claims 49-52 were withdrawn from consideration as being drawn to a non-elected invention in the previous office action. Claims 53-55 are newly added, and fall within the elected group I.

3. Applicant's election with traverse of Group I, claims 40-48, and new claims 53-55 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the searches for groups I-III would be coextensive in scope, and that groups I-III are not patentably distinct from one another as groups II and III require the polynucleotides of group I. This is not found completely persuasive because the claims of Group II are to a different composition (polynucleotide plus liposome), and a system of delivery to a patient, while the claims of group I are directed solely to the polynucleotide composition. Methods of treating a patient would not necessarily be illuminated by a search for antisense polynucleotides, as antisense technology has uses in tissue culture and other non-patient systems. Even with the antisense polynucleotides being in a pharmaceutical composition, they can still be used as probes, and primers for PCR, as set forth in the previous office action. Applicant's arguments in regard to Group III are persuasive, and claim 52 will be examined in this action.

4. In view of Applicant's amendments or arguments, the following objections or rejections are withdrawn:

The rejection of claims 40-48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

5. Claims 40-45 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,714,596. Although the conflicting claims are not identical, they are not patentably distinct from each other because the oligonucleotides of the '596 patent fulfill the limits of claims 40-45, as an oligonucleotide can be used as an antisense nucleotide, and an antisense polynucleotide can be use as an oligonucleotide. The chemical compositions are the same, and the recitation of "antisense" is merely a statement of intended use. Likewise, the recitation of "pharmaceutical composition" and "pharmaceutically acceptable excipient" do not distinguish over the claims of the patent, as the excipient could be water, saline or other liquid in which one would fine the "purified preparation of an oligonucleotide" as in the '596 patent.

6. Claims 40-48 and 52-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous office action.

Claims 40-48 are drawn to pharmaceutical preparations of antisense oligonucleotides of varying lengths which may have altered bonds, or chemical entities attached to them. Claims 40-44 set forth lengths from 8 to 20 nucleotides for the antisense oligonucleotides. New claims 53-55 set forth the antisense oligonucleotide composition also comprises an agent which causes viral RNA to be inactive. Claim 52 is drawn to a method of using the polynucleotide of claim 40 for inhibition of viral replication.

Applicant argues that the recitation at page 78 of the specification is sufficient teaching of what portions of the genome antisense molecules should target, however there is no indication of what regions of DNA would be useful in targeting such activities as the broad recitation of "block protein translation" and "prevent viral replication". No portions of the HCV genome which would be useful to prevent or block these viral replications steps are indicated or even hinted at in the specification. The information recited in section II.H does not further illuminate how to chose antisense polynucleotides which would block or prevent protein translation or viral replication. Section II.H deals with the selection of probes and primers, which would not necessarily perform any antisense functions.

Each of the sections pointed out by Applicant are vague prophetic recitations which indicate that antisense polynucleotides could be found or identified, however, no such antisense polynucleotides are taught in the specification.

Legal precedence dictates that conception of a chemical compound, such as a DNA molecule, is not achieved until reduction to practice has occurred. (*Amgen Inc v. Chugai*

Pharmaceutical Co. Ltd 18 USPQ2d 1016-1031 (CAFC 1991); *Fiers v. Revel* 25 USPQ2d 1601-1607 (CAFC 1993)). At no point in the file history of this application are specific antisense polynucleotides set forth. In *Amgen Inc v. Chugai Pharmaceuticals Co. Ltd* 18 USPQ2d 1016 (CAFC 1993) the court ruled that:

> Conception of a chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property; thus, when inventor of gene, which is chemical compound albeit complex one, is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until after gene has been isolated.

The court further elaborated on this point and concluded that:

> A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka*, 849 F2d at 583 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its methods of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoetin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. (emphasis added)

Applicant has pointed to recitations in the specification indicating that antisense polynucleotides could exist, and could be identified, however, none were identified. These

arguments are analogous to the above recited "wish to know the identity" of effective antisense polynucleotides of HCV.

The significance of conception and reduction to practice was further addressed by the court in *Fiers v. Revel* 25 USPQ2d 1601-1607 (CAFC 1993):

> Conception is question of law, reviewed de novo on appeal, and if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated; thus, regardless of complexity or simplicity of method of isolation employed, conception of DNA sequence, like conception of any chemical substance, requires definition of that substance other than by its functional utility. (emphasis added)

In the instant application, Applicants have identified a single HCV isolate, therefore disclosing the genomic sequence for that strain. Applicant has not provided guidance as to what portions of the genome would be useful as antisense polynucleotides. The prior art does not provide any antisense polynucleotides of HCV, and the skilled artisan could not predict those sequences. The unpredictability of the antisense art is further illustrated by Branch, A.D. A good antisense molecule is hard to find. 1998 TIBS vol 23 pp 45-50) Branch reviews the many problems inherent in selecting antisense molecules which will target the intended processes in vitro and in vivo. Branch even speaks specifically to problems with antisense technology as it relates to HCV at page 48:

> "One anecdote reveals how the redundancy of biological sequences could plague antisense methods. A conserved region at the 5' end of the hepatitis C virus is considered to be a potential target for antisense drugs. This short region

contains a particular 10-mer that is also present in 62 known human mRNAs (citation omitted), and it contains two 17-mers that occur in known human DNA sequences."

The specification, as filed, does not point out oligonucleotides of 8, 10, 12, 15 or 20 nucleotides that would be suitable for use as antisense polynucleotides. There is no direction as to which sequences should be selected from the approximately 9Kb of HCV sequence. There is no teaching as to which portions of the HCV genome would be susceptible to an antisense blockage and therefore a suitable region from which the polynucleotide could be selected, nor is there an indication as to what length of oligonucleotide is preferred. There is no recitation of particular sequences of polynucleotides useful in the practice of the invention. It is apparent that the polynucleotides may comprise other, non-HCV sequences, as long as there is a stretch of HCV sequence within, which further broadens the scope of the claims. The very large number of potential polynucleotides covered by the scope of the pending claims is an invitation to experiment with the 9000+ nucleotides of HCV-1 and any other HCV or non-HCV sequence, to find polynucleotides which are capable of acting as antisense polynucleotides in the practice of the invention.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 8:00 am and 5:30 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
August 27, 1998

MICHAEL P. WOODWARD
PRIMARY EXAMINER
ART UNIT 1643